Decision Memo for Cardiac Pacemakers (CAG-00063N)

Decision Summary

We will maintain the current non-coverage policy. Medicare will not cover pacemaker implantation for either post MI patients with asymptomatic bradycardia who otherwise would be precluded from beta-blocker long-term drug therapy or post MI patients who are treated with beta-blockers and later develop asymptomatic bradycardia as a result of the treatment. Medicare will continue to cover pacemaker implantation in patients with symptomatic bradycardia whether iatrogenic or induced by required pharmacologic therapy.

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Decision Memo

To: Administrative File CAG-00063N: Cardiac Pacemakers

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Subject: National Coverage Decision

Date: March 20, 2001

This memo serves four purposes: (1) provides background on acute myocardial infarction (MI), pacemakers and beta-blocker drug therapy; (2) reviews the history of Medicare's coverage process on pacing for patients with symptomatic and asymptomatic bradycardia and provides a timeline of recent activities; (3) presents and analyzes the relevant scientific and clinical data related to these patient populations; and (4) delineates the reasons for making the coverage decision.

Clinical Background

Acute Myocardial Infarction

Coronary artery disease, a major cause of MI, is a serious health problem in the United States. It affects approximately seven million Americans and annually accounts for 750,000 hospital admissions and more than 500,000 deaths.[1] Coronary artery disease can lead to inadequate tissue oxygenation, a state known as ischemia. When this decrease in perfusion occurs and is not alleviated, that section of myocardium progresses to permanent damage and cell death. This process is referred to as myocardial infarction.

Frequent signs and symptoms of ischemia and/or infarction are:

- chest pain or pressure,
- arrhythmias,
- congestive heart failure,
- hypotension or shock,
- nausea, diaphoresis and/or other atypical symptoms.[2]

Heart attack survivors are at an increased risk of experiencing a second MI or other cardiac event; this population has a death rate of 10% in the first year post MI, and 5% in each additional year.[3] Several medications are effective in reducing the risk of reinfarction in post MI patients, such as aspirin, beta-blockers and lipid lowering agents.

Pacemakers

Pacemakers are generally implanted to alleviate symptoms of decreased cardiac output related to rate or arrhythmia. It is essential to document an association between symptoms and the dysrhythmia before pacemaker implantation because symptoms may be non-specific, such as dizziness or lightheadedness. Less than 2% of patients suffer from complications due to pacemaker implantation. Examples of complications include pneumothorax, perforation of the atrium or ventricle, lead dislodgement, infection and erosion of the pacemaker pocket. In addition, pacemaker batteries typically have a life span of seven to eight years, which means that the implanted patient will eventually need to endure a second invasive procedure in order to replace the battery. Pacemakers are generally used for persistent, symptomatic second- or third-degree AV block and symptomatic sinus bradycardia. For some patients, it may be appropriate to implant a pacemaker in order to continue pharmacologic treatment.[4]

Beta-Blocker Treatment

Beta-blockers are a beneficial treatment for post MI patients because they decrease the incidence of recurrent cardiac events by blunting the effects of adrenaline in the body. Beta-blockers slow an individual's heart rate, decrease myocardial contractility, and lower blood pressure, thus lessening the heart's overall workload and decreasing its demand for oxygen.[5] Further, beta-blockers reduce infarct size in patients with acute MI and decrease the risk of sudden death due to ventricular arrhythmias. Clinicians increasingly understand that beta-blockers are an important treatment for patients post MI. An article by Hjalmarson (1997) claims that there is no other therapy that has such a well-documented effect on sudden cardiac death.[6]

Many MI patients have demonstrated a benefit from beta-blockers. Gottlieb et al.[7], found that patients treated with beta-blockers had substantially lower mortality than patients who were not. For patients with MI and no other complications, treatment with beta-blockers was associated with a 40% reduction in mortality. This trend was also found for patients with non-Q-wave infarction and those with chronic obstructive pulmonary disease. However, the authors also acknowledge that patients who have contraindications may not benefit from beta-blocker drug therapy to the same extent as was demonstrated in this study. In addition, a Quality Care Alert[8] developed by five specialty societies, including the American Association of Clinical Endocrinologists, the American Academy of Family Physicians, the American College of Physicians/American Society of Internal Medicine, American Psychiatric Association, and the American College of Cardiology, reports that beta-blockers are both scientifically and medically substantiated. Beta-blockers have been shown to decrease both cardiovascular mortality and reinfarctions.

A number of studies have documented underutilization of beta-blockers. Underutilization is defined as not prescribing beta-blockers or prescribing at lower doses than found beneficial in clinical trials. Underuse among Medicare patients who are post MI is associated with multiple factors, including geographic location, co-morbid disease state, and prescription of other agents (specifically calcium channel-blockers).[9] The American College of Cardiology (ACC) and the American Heart Association (AHA) Guidelines for the Management of Patients with Acute Myocardial Infarction recommend that survivors of myocardial infarction be treated with long-term beta-blockers, provided that they do not have one of the following relative contraindications:[10]

- Heart rate less than 60 beats per minute (bpm),
- Systolic arterial pressure less than 100 mm Hg,
- Moderate left ventricular failure,
- Signs of peripheral hypoperfusion,
- PR interval greater than 0.24 second,
- Second- or third-degree atrioventricular (AV) block,

- Severe chronic obstructive pulmonary disease,
- History of asthma,
- Severe peripheral vascular disease or
- Insulin-dependent diabetes mellitus.

The guidelines further state that patients with certain relative contraindications may still benefit from beta-blockers. These contraindications are:

- Moderate left ventricular failure,
- PR interval greater than 0.24 second,
- Severe chronic obstructive pulmonary disease,
- History of asthma,
- Severe peripheral vascular disease or
- Insulin-dependent diabetes mellitus.

It is notable that patients with heart rate less than 60 bpm are not listed within a group that may experience benefit from beta-blockers.

Beta-Blocker Dosage

Typically eligible patients are titrated with B-blockers until clinical B-adrenergic blockade is achieved. A clinician may select a clinical variable, such as a target heart rate, as a guide to drug dosing. In addition, " . . . clinical judgement is usually the primary determinant of the adequacy of a given heart rate response to administration of beta-adrenoreceptor antagonists, with consideration given to a patient's overall cardiovascular state."[11]

History of Medicare's Coverage of Cardiac Pacemakers

The United States Food and Drug Administration (FDA) Approval

The Medical Device Amendments Act to the Federal Food, Drug, and Cosmetic Act established three regulatory classes of medical devices. These classes are listed below:

Class I: Devices for which the general controls of the Food, Drug, and Cosmetic Act, such adherence to good manufacturing practice regulations, are sufficient to provide a reasonable assurance of safety and effectiveness.

Class II: Devices that, in addition to general controls, require special controls, such as performance standards or postmarket surveillance, to provide a reasonable assurance of safety and effectiveness.

Class III: Devices that cannot be classified into Class I or Class II because insufficient information exists to determine that either special or general controls would provide reasonable assurance of safety and effectiveness. Class III devices require premarket approval.[12]

The class to which a device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If a device is classified as Class I or II, and if it is not exempt, a 510k will be required for marketing. For Class III devices, a premarket approval application (PMA).[13] Pacemakers that are currently developed which are considered similar to predicate devices are cleared through the 510k process.

Pacemaker lead submissions can be supported by both non-clinical and clinical tests. Non-clinical tests include: biocompatibility, animal studies, bench testing and insulation characterization and biostability. Clinical data are not necessary to support market clearance of permanent pacemaker leads. However, the following components are considered in reviewing clinical tests: study design, study endpoints, criteria for lead-related complications and failures, methods of lead safety analysis and steroid pacing leads. These tests are used to evaluate a device for safety, effectiveness and clinical utility. The FDA acknowledges that non-clinical testing is usually sufficient to support substantial equivalence of a pacemaker lead adapter in a PMA submission and/or premarket notification (510(k)).[14]

The FDA approves pacemakers for a variety of indications. Indications vary from device to device; however, they can be grouped into six general categories: sino-atrial node dysfunction (e.g. sinus bradycardia, sinus arrest); AV node dysfunction including 2nd or 3rd degree AV node block and bundle branch block; chronotropic incompetence (e.g. insufficient heart rate during exercise); bradycardia-tachycardia syndrome; and certain types of neuro-vascular syndromes which would effect the cardiovascular system (e.g. hypersensitive carotid sinus syndrome; and certain types of syncope of cardiac origin).

Current Coverage Issues Manual (CIM) Policy

The complete cardiac pacemaker policy is located in Section 65-6 of the Coverage Issues Manual; it was last updated in 1985. This policy limits the number of conditions HCFA will pay for a cardiac pacemaker. Although Medicare does not cover pacemaker insertion for patients with asymptomatic bradycardia, Medicare does cover pacing for beneficiaries with symptomatic bradycardia. Section 65-6, Part A, describes a condition that is generally considered necessary for cardiac pacemaker implantation:

"Sinus bradycardia which is the consequence of long-term necessary drug treatment for which there is no acceptable alternative, when accompanied by significant symptoms (e.g., syncope, seizures, congestive heart failure, dizziness or confusion). The correlation between symptoms and bradycardia must be documented, or the symptoms must be clearly attributable to the bradycardia rather than to some other cause."[15]

Section 65-6, Part B, specifically states that insertion of pacemakers for patients with "Sinus bradycardia without significant symptoms," is not covered by Medicare.

Coverage Request

In June 2000, Medtronic requested that HCFA review the use of a pacemaker to treat:

1. Post MI patients with asymptomatic bradycardia who otherwise would be precluded from beta-blocker long-term drug therapy; and
2. Post MI patients who are treated with beta-blockers and later develop asymptomatic bradycardia as a result of the treatment.

As part of the request, Medtronic included a suggested definition of asymptomatic bradycardia in post-MI patients. The definition is patients with one of the following conditions:

a. Resting (awake) heart rate less than or equal to 50 beats per minute on 2 consecutive days in the absence of treatment with rate-slowing medications (i.e., diltiazem, verapamil);
b. Sinus pauses (greater than 2 seconds) during the day;
c. PR interval greater than or equal to 280 msec in the absence of medications that prolong AV nodal conduction time (digoxin, diltiazem, verapamil); or
d. Second-degree AV block, type I at rest (and awake).

ACC/AHA Recommendation

The ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices were established to assist physicians in clinical decision-making and are revised periodically. This document was designed to provide general guidance to practicing physicians. Class I recommendations are conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful and effective. Level C evidence is a consensus opinion of experts. The following is a Class I recommendation supported by Level C evidence:

*Sinus Node dysfunction with documented **symptomatic** bradycardia, including frequent sinus pauses that produces symptoms. In some patients, bradycardia is iatrogenic and will occur as a consequence of essential long term drug therapy of a type and dose for which there are no acceptable alternatives.*[16]

It is notable that the ACC/AHA guidelines do not explicitly recommend pacemaker insertion for post MI patients with asymptomatic bradycardia who are either treated with beta-blockers or being considered for beta-blocker therapy.

Recent Developments and Timeline of Activities

June 7, 2000	HCFA receives Medtronic's request for reconsideration.
June 10, 2000	Letter sent to Medtronic officially accepting the request.
August 9, 2000	After reviewing Medtronic's request, HCFA concluded that additional information would be helpful in the analysis. The following questions were posted on the HCFA website.

1. The ACC recommendation is for symptomatic, iatrogenic bradycardia. What is the rationale for use in asymptomatic patients who may begin beta-blocker therapy?

2. What is the evidence that post MI patients with bradycardia benefit from beta-blocker therapy?

3. One proposed definition of asymptomatic bradycardia includes post MI patients with one of the following documented conditions:

a. Resting (awake) heart rate less than or equal to 50 beats per minute on 2 consecutive days in the absence of treatment with rate-slowing medications (i.e., diltiazem, verapamil)

b. Sinus pauses (greater than 2 seconds) during the day

c. PR interval greater than or equal to 280 msec in the absence of medications that prolong AV nodal conduction time (digoxin, diltiazem, verapamil)

d. Second-degree AV block, type I at rest (and awake)

Is this a reasonable definition?

August 30, 2000	HCFA received a joint letter from the North American Society for Pacing and Electrophysiology (NASPE) and the ACC (together, these organizations represent over 25,000 cardiologists) and a letter from a cardiologist. Due to the low response rate to these important questions, we decided to extend the deadline to October 5, 2000.
November 7, 2000	HCFA was notified by the requestor of plans to submit additional information. For this reason, a new deadline was contingent upon receipt and review of the information.
November 8, 2000	HCFA met with Medtronic representatives.
December 9, 2000	Additional relevant information was provided by the requestor. The decision due date was extended to February 20, 2001, in order to review this material.

Summary of Evidence

In addition to the articles submitted by Medtronic, which can be found in Attachment 2, HCFA staff conducted a comprehensive literature search. We first reviewed the ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices.[17] We did a Medline search using the following terms: beta-blockers, myocardial infarction, elderly, cardiac pacemakers and ACE-inhibitors.

Medtronic, Inc. submitted a total of 21 pieces of literature, of which 13 were included in our analysis and the remaining eight were excluded. There are numerous reasons why we excluded articles from our analysis. For example, one article excluded patients who suffered from a recent MI; a second article excluded patients with high degree AV block. A third article focused on advancements in pacemaker technologies and not pacing for asymptomatic bradycardic patients. In addition to the inclusion and exclusion tables (Attachments 3 [PDF, 96KB] and 4 [PDF, 77KB], respectively), details from each article analyzed are provided in Attachment 1.

We could not find any direct evidence that post-MI asymptomatic bradycardic patients receive benefit from beta-blockers. The available studies generally exclude patients with contraindications, such as asymptomatic bradycardia. Studies that do address broader populations generally enroll small numbers of contraindicated patients and do not provide adequate subgroup analyses. Therefore, we are unable to generalize the results from these studies to the asymptomatic bradycardic population.

For patients with asymptomatic bradycardia, beta-blockers may cause problems other than low heart rate. For example, they also blunt the tachycardic response to stressors such as exercise, dehydration or sepsis.[18] The authors of a NEJM[19] editorial write, "Beta-blockers could provide substantial protection from future cardiac events, but relative contraindications could increase some patients' vulnerability to the adverse effects of the therapy. We lack critical information necessary to determine the balance of risk and benefit for beta-blockers with respect to the large population of mostly older patients with relative contraindications to therapy."

One study we reviewed investigated the effects of beta-blockade on patients with heart failure.[20] This double-blind, placebo-controlled, randomized trial illustrates that it is possible to generate direct evidence about the benefits of beta-blockers in a population previously considered to be contraindicated. We could find no such evidence for post MI patients with asymptomatic bradycardia.

In response to the questions posted on the HCFA website on August 9, 2000, we received two timely responses to the questions. The first was from a clinician at Northwestern University. There was consensus among his colleagues that patients exhibiting certain conditions (i.e., 50 bpm or less) would not generally be treated with beta-blockers. He also stated that a pacemaker would need to be implanted for such patients to begin beta-blocker treatment. In a follow-up telephone conversation, he stated his belief that Medicare coverage should include pacemaker implantation for the post MI patient with asymptomatic bradycardia who potentially could be treated with beta-blockers.

The second response was submitted jointly by the NASPE and the ACC. In the joint response, these organizations supported the Medtronic request by stating, "Pacemaker implantation is recommended in this situation [patients with asymptomatic bradycardia] to prevent the iatrogenic symptomatic bradycardia that will occur once the drug therapy [beta -blockers] is started. For the small subset of patients who will experience symptomatic bradycardia upon the initiation of long-term drug therapy, this is an extension of the recommendations for treatment of currently symptomatic bradycardia."

However, the NASPE/ACC advised that HCFA use the ACC/AHA published recommendations[21] as relative contraindications to beta-blocker therapy rather than Medtronic's definition of asymptomatic bradycardia. These contraindications include: heart rate less than 60 bpm, PR interval greater than 240 msec and second or third degree AV block. The response also included the statement that "Due to the overwhelming evidence in favor of beta-blocker therapy following myocardial infarction, the 1999 update of the ACC/AHA guidelines state that every patient following myocardial infarction has either a class I or class II indication for beta blockers." The actual language in the 1999 update of the guideline for Long-Term ß-Adrenoceptor Blocker Therapy in Survivors of Myocardial Infarction reads:

Class I:	All but low-risk patients without a clear contraindication to ß-adrenoceptor blocker therapy.
Class IIa[22]:	1. Low-risk patients without a clear contraindication to ß-adrenoceptor blocker therapy 2. Survivors of non-ST elevation MI

Class IIb:	Patients with moderate or severe LV failure or other relative contraindication to ß-adrenoceptor blocker therapy, provided patients can be monitored closely.

These guidelines make no recommendations regarding use of pacemakers to allow use of beta-blockers in bradycardic patients, nor do they comment specifically on the benefits or risks of beta-blockers in post-MI patients with bradycardia.

HCFA Analysis

Medtronic has requested two specific indications for coverage of pacemaker implantation:

1. Post MI patients with asymptomatic bradycardia who otherwise would be precluded from beta-blocker long-term therapy; and
2. Post MI patients who are treated with beta-blockers and later develop asymptomatic bradycardia as a result of the treatment.

Medtronic's principal rational for implanting pacemakers in post-MI patients with asymptomatic bradycardia is that they might better tolerate long-term beta-blocker therapy. All studies point to a clearly demonstrated long-term benefit to beta-blocker therapy for post MI patients **without** bradycardia. When beta-blockers are administered to patients without contraindications, part of their beneficial effect is due to slowing the heart rate to decrease the work of the heart. Typically dosage is titrated until a target heart rate is achieved. Patients who have asymptomatic bradycardia already experience a slowed heart rate, similar to the chronotropic effect of beta-blockade, without ever receiving beta-blocker therapy. Although beta-blockers may decrease sudden and non-sudden cardiac death through other mechanisms in addition to slowing the heart rate, it is unknown what benefit beta-blockers have on the bradycardic population since these persons were excluded in all known studies. For this reason, it is unclear whether the evidence reflecting patients without contraindications is generalizable to patients with specific contraindications. In addition, the risks of beta-blocker therapy in bradycardic post MI patients are unknown; therefore it is unknown whether the benefits of beta-blocker therapy in this group are outweighed by increased risks, including sudden death.

The NASPE and the ACC recommended in their joint letter that HCFA cover pacing for patients with heart rate less than 60 bpm and stated that all post-MI patients are included in either a class I or class II recommendation supportive of treatment with beta-blockers. However, the evidence-based guidelines did not include patients with heart rates less than 60 bpm, even in the list of relative contraindications once thought to preclude use of beta-blockers. Additionally, the recommendation for post-MI patient with relative contraindications to beta-blockers was a class IIb recommendation. This level of recommendation is weak; the level is applied when the "usefulness/efficacy is less well established by evidence/opinion."

The evidence was also insufficient to suggest a benefit from pacemaker implantation for patients who develop asymptomatic bradycardia as a result of beta-blocker therapy. We understand that a physician may discontinue beta-blockers for these patients with the belief that a patient may eventually develop symptomatic bradycardia. It is possible however, that these patients will never develop symptoms from bradycardia. Thus, the risks of implantation for all patients that develop asymptomatic bradycardia must be weighed against the **potential** benefits that would be gained in the patients that might develop symptoms. For those patients that develop symptoms, Medicare already reimburses pacemaker implantation. The benefit of prophylactic pacemaker placement in those that remain asymptomatic is unknown. There is no demonstration of beneficial placement in this group.

Although studies do not exist supporting beta-blocker use for post MI patient with asymptomatic bradycardia, a study of similar design has been successfully conducted in the heart failure population.[23] This design could reasonably be done with the populations in question here to provide evidence of long-term benefit.

Unfortunately, underutilization of beta-blockers in appropriate and eligible patients is well documented.[24] However, this under use is for patients appropriate and eligible for therapy, not those with contraindications to beta-blocker use in which benefit is not demonstrated. There are currently efforts underway at HCFA to increase the rate of beta-blocker use in eligible patients.[25] Underutilization in appropriate patients is not a rationale for pacing contraindicated patients.

Lastly, we examined whether there could be other benefits associated with pacemaker implantation for post-MI patients with asymptomatic bradycardia. The evidence reviewed, however, was insufficient to demonstrate that there were any additional benefits for this patient population. Therefore, we cannot make a determination that pacemaker implantation is reasonable and necessary for such patients.

In summary, the central question underlying the medical benefits of pacemakers in this population is whether or not patients who are post MI and have bradycardia would benefit from beta-blocker therapy. No direct evidence on this question exists, since such patients were excluded from all clinical trials. The rates of severe adverse events in bradycardic post MI patients treated with beta-blockers are also unknown. The small but nontrivial risks associated with pacemaker insertion and chronic usage are well characterized. Until more evidence is available or evidence-based clinical standards are issued on the net medical benefit of beta-blockers in this patient population, pacemaker implantation is not considered reasonable and necessary in these circumstances.

Decision

We will maintain the current non-coverage policy. Medicare will not cover pacemaker implantation for either post MI patients with asymptomatic bradycardia who otherwise would be precluded from beta-blocker long-term drug therapy or post MI patients who are treated with beta-blockers and later develop asymptomatic bradycardia as a result of the treatment. Medicare will continue to cover pacemaker implantation in patients with symptomatic bradycardia whether iatrogenic or induced by required pharmacologic therapy.

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Class IIa recommendations are made when the "weight of evidence/opinion is in favor of usefulness/efficacy.
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